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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/780,675	02/12/2001	Nicholas C. Nicolaides	01107.00098	8276

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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 12/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

12/27/04 14

Office Action Summary	Application No.	Applicant(s)	
	09/780,675	NICOLAIDES ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-7,16-18,26-27 and 71-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,7,16-18,26,27 and 71-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of a response/amendment, filed 10/15/2004, is acknowledged. Claims 1,6, 7,16-18, 26-27 and 71-78 are pending and under consideration. All objections/rejections not repeated herein are hereby withdrawn. Where applicable, a response to applicant's arguments with respect to any objection/rejection maintained is included in the body of such objection/rejection, which is repeated herein. As no new grounds of rejection are set forth, **this action is made FINAL.**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Claims 1,6, 7,16-18, 26, 27 and 71-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.**

This rejection is of record and is repeated in salient part herein. A response to applicant's arguments is set forth immediately below. (Infra, Response to Arguments). The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims are drawn to methods for making hypermutable bacterium by introducing into bacterium a polynucleotide encoding any dominant negative PMS2 mismatch repair protein or truncations thereof or encoding any PMSR or PMS2L mismatch repair protein, whereby expression of such protein confers a dominant negative effect

on mismatch repair resulting in hypermutable bacterium. More particularly, the claims encompass any PMS2 truncation (claims 1 and 8), any human PMS2 truncation (claim 6), any plant PMS2 truncation (claim 7), a PMS2-134 truncation from any source (claims 26 and 71), any PMSR or PMS2L (claim 72) and any PMS2 truncation from *A. thaliana* (claim 76). Moreover, expression of said proteins is expected to induce hypermutability in any bacterial organism. Therefore, either knowledge in the art or applicant's disclosure must show that the various embodiments within the claimed genera of any truncated PMS2 proteins, any PMSR or any PMS2L inhere a structure to function correlation. The critical structural requirement of the invention is that any protein from the PMS2, PMSR and PMS2L family of proteins (or truncated versions of PMS2), when expressed in any bacterium, must interact with the host bacterial mismatch repair mechanism so as to exert a dominant negative effect resulting in a hypermutability.

The written description for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosures of relevant identifying characteristics, i.e. structure or physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus. Moreover, the written description requirement is grounded in the concept of predictability viz., structure to function correlation, with respect to different species within a genus. Put another way, the disclosure is sufficient when substitution of a disclosed species with an undisclosed species would result in a predictable outcome.

The specification teaches that expression of a human homologue to bacterial MutL – hPMSR3, in *E. Coli* causes hypermutability (Example 2) and two PMS2 truncation mutants (codon 134) from human and plant that exert a dominant negative effect when expressed in bacteria (Example 3). Therefore the specification does not provide clarification of various truncated versions of PMS2 from a single species (e.g. human) that function to induce hypermutability in bacteria, whether the truncations are from a single species of organism or from disparate species of organisms. Furthermore, with respect to truncated versions, only a single truncation is provided (i.e. codon 134) for a single mismatch protein (hPMS2 and plant PMS2), which would not necessarily be predictive of all truncated versions, or for that matter, all codon-134 truncations of PMS2 protein from different organisms.

There is no evidence in the art to show that the various claimed genera would operate in similar fashion. Evidence shows that members within the highly conserved human family of mismatch repair proteins may not be involved in mismatch repair at all. For example, highly conserved species within the family of PMS2L proteins do not interact with a major DNA mismatch repair protein – hMLH1. (Kondo et al. J. Biochem. 1999; 125: 818-825; Abstract), similar to hPMS2-134. However, although citing the structural similarity between the PMS2Ls studied and hPMS2, Kondo et al. does not conclusively provide that PMS2Ls, expressed in mammalian cells (or bacteria), would necessarily lead to hypermutability. Indeed, Kondo et al. state:

> "[PMS2Ls] may also be involved in the downstream pathway of the human MMR system or they may have a completely different role(s) in the [human] cell. *If* the former possibility is true, the abnormal expression of *some* PMS2Ls may give rise to defects in the MMR pathway. Analysis of the proteins interacting with PMS2Ls may lead to the elucidation of the function of PMS2Ls or of the downstream pathway in the MMR system.[emphasis added] (p. 824, col. 2, last ¶).

Therefore, Kondo et al. clearly teach that further clarification of any structure to function correlation is needed and that one PMS2L is not necessarily equivalent in functionality (i.e. affecting downstream pathways in the MMR system) as compared to another. In other words without clarification of what domains that are necessary and identification of the boundaries for said domains in a particular PMS2L mismatch protein, one of skill would not be able to envisage all embodiments encompassed by the broad genera of mismatch proteins claimed. Indeed, as is acknowledged in the art, even highly conserved mismatch repair proteins may have completely different roles in a cell, rather than involvement in mismatch repair mechanisms. (Id. at col. 2, last ¶). Furthermore, with respect to all PMSR genes, the function for PMSR genes is not definitively known (See Nicolaides et al. Genomics, 1995; 20:195-206; p. 205; reference of record), thus a result for a single member of the PMSR family (i.e. hPMSR3, Example 3) would not necessarily be predictive to other proteins having the prescribed functionality.

Therefore, it would be evident to one of ordinary skill in the art that applicant is not in possession of the claimed invention. Given the enormous breadth of the mismatch repair proteins encompassed by the rejected claims (i.e. PMS2, PMSR, PMS2L and PMS2-134), and given the limited description from the instant specification of such in light of the what is known in the art, the skilled artisan would not have been able to envision a sufficient number of specific embodiments to described the broadly claimed genus of mismatch repair proteins. Moreover, an applicant claiming a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species, because there may be unpredictability in the results obtained from other species. Therefore, the skilled artisan would reasonably have concluded that applicants were not in possession of the claimed invention.

Response to Arguments

Applicants' arguments have been considered but are not deemed persuasive. Applicants' arguments are limited to showing why the teachings of Prudhomme et al. and Kondo et al. are not indicative of unpredictability of the various embodiments/genera encompassed by the claims. (Remarks, pp. 6-8). First, Applicants asset that Prudhomme et al. is limited to showing that HexB, a *Streptococcus pneumonia* homologue of the *Escherichia coli* MutL protein, when expressed in *E. coli* does not induce hypermutability, but that such a showing is not germane to PMS2, PMSR or PMS2L proteins (from any organism) when expressed in bacteria. Put another way, Applicants assertion can be interpreted to mean that using homology as between bacterial species is would not indicate predictability as to structure to functional correlation between PMS2 truncated proteins, or various proteins from the family of PMSR or PMS2L proteins. Applicants are discounting use of homology of MutL proteins as between two bacterial species to show unpredictability as between various embodiments within genera, but concomitantly contend that hPMS2 – a human MutL homologue – or PMS2 from any source would be expected to function the same in any bacterial species to induce hypermutability.

One of skill in the art would recognize if proteins from relatively closely related organisms do not show a structure to function correlation, then certainly the level of unpredictability for such structure to function correlation would be exacerbated as between evolutionarily more distinct organisms (e.g. human, plant and bacteria). Therefore, Applicants' assertion that Prudhomme et al. has not bearing on the patentability of the present claims is deemed unpersuasive. (Remarks, p. 6, ¶ 3).

Indeed, Prudhomme et al. teachings are interpreted to mean that simple homology cannot be used to predict structure to function correlations for MMR proteins that are MutL homologues (i.e. PMS2). Moreover, Applicants have not presented any arguments as to why truncated versions of any PMS2 proteins or a PMS2-134 protein from any organism would be expected to function similarly in bacteria to induce hypermutability (by affecting the MMR system in bacteria).

Applicants next assert that Kondo et al. shows the structural similarity between PMS2Ls and hPMS2-134 with respect to binding hMLH1. (Remarks, p. 7). As noted in the foregoing, MMR homologues in more closely bacterial organisms do not function similarly. Furthermore, without further clarification of structure to function correlations, as noted above with respect to what Kondo et al. teach, mere structural homology does not provide that PMS2Ls would necessarily function to induce mutations when expressed in human cells, not to mention bacterial cells, as Applicants claim. For example, a single amino acid truncation could impart a different functional profile for a given PMS2L protein when expressed in bacteria and such a result could be altogether different depending on the host cell wherein the protein is expressed. In sum, Kondo et al. stands for the assertion that PMS2Ls are unknown in function and even if through biochemical studies such function were resolved as to particular proteins within the hPMS2L family, such a result would not necessarily indicate how other members of the PMS2L family would function. Similarly with respect to PMSR proteins, with respect to all PMSR genes, the function for PMSR genes is not definitively known (Supra, Nicolaides et al. 1995; p. 205), thus a result for a single member of the PMSR family (i.e. hPMSR3, Example 3) would not necessarily be predictive to other proteins having the prescribed functionality.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 16, 17 and 71 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-3 and 36 of copending Application No. 09/912,697.

This rejection is of record and will not be repeated herein. Applicants have noted the rejection, have not presented any arguments in traversal, but have chosen to request abeyance. As indicated above, this provisional rejection is not the only remaining issue, thus the rejection is made final.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached between 8:30-5:00, Monday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

GERRY LEFFERS
PRIMARY EXAMINER